

## ORIGINAL ARTICLE

## Primary prevention of latex related sensitisation and occupational asthma: a systematic review

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**Methods:** Eight primary prevention intervention studies on natural rubber latex (NRL) published since 1990 were identified and reviewed. This is the largest evidence base of primary prevention studies for any occupational asthmagen.

**Results:** Review of this small and largely observational evidence base supports the following evidence statement: Substitution of powdered latex gloves with low protein powder-free NRL gloves or latex-free gloves greatly reduces NRL aeroallergens, NRL sensitisation, and NRL-asthma in healthcare workers. Evidence in support of this statement is ranked SIGN level 2+, referring to well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.

**Conclusion:** Substitution of powdered latex gloves with low protein powder-free NRL gloves or latex-free gloves promises benefits to both workers' health and cost and human resource savings for employers. This message should be broadly disseminated beyond the hospital sector to include other healthcare settings (such as aged care facilities) as well as food service and other industries where latex gloves might be used.

Primary prevention of occupational asthma refers to the prevention or control of exposure to asthmagenic agents and conditions in the workplace. Secondary prevention involves early detection through medical screening and intervention. Finally, tertiary preventive intervention involves the management of occupational asthma to limit disability, impairment, and the related socioeconomic impacts. There has been a rapid growth in scientific and medical understanding of occupational asthma over the last two decades, particularly in understanding the causative agents and mechanisms, detecting early signs of occupational asthma, and how to clinically manage the disease.<sup>1</sup> Primary prevention of occupational asthma, however, has received far less research attention, despite primary level intervention being the most desirable from a public health perspective.

Accordingly, we set out to systematically review the evidence that primary prevention of occupational asthma was effective. During the course of our study, a systematic review was published by Nicholson *et al*, detailing evidence based guidelines for the prevention, identification, and management of occupational asthma.<sup>1</sup> Having evaluated essentially the same evidence base, we concur with the two primary prevention evidence statements generated from that review.<sup>1</sup> The first concerns source focused primary prevention, and the second acknowledges a role for worker focused primary prevention (respirator use):

- "Reducing airborne exposure reduces the number of workers who become sensitised and who develop occupational asthma"; evidence rating: Scottish Intercollegiate Guidelines Network (SIGN) 2+ (Evidence Statement 16 in Nicholson *et al*, 2005<sup>1</sup>)
- "The use of respiratory protective equipment reduces the incidence of, but does not completely prevent, occupational asthma"; evidence rating: SIGN 3 (Evidence Statement 17 in Nicholson *et al*, 2005<sup>1</sup>).

This report details a new evidence statement to add to the two above. It is based on a larger number of primary

prevention studies on natural rubber latex than were reviewed by Nicholson *et al*.<sup>1</sup> We present comprehensive search and critical review strategies, followed by review findings, the resulting evidence statement, and a brief discussion of implications for policy and practice.

## METHODS

## Literature search

The literature search was conducted using OSH-ROM (incorporating RILOSH and HSELINE), TOXLINE, MEDLINE, and CINAHL databases. Secondary follow up of sources cited in reference lists was also undertaken. Databases were searched systematically from 1990 up to September 2004, restricting the search for the following two sets of keywords to the title and abstract fields:

- Keywords describing the respiratory outcome: occupational asthma, occupational respiratory disease, and work related asthma
- At least one of the following intervention related keywords: policy, regulation, exposure control, prevention, hygiene, and intervention.

Search results were reviewed and relevance of papers was determined by considering the abstract or the full text of each article. We restricted our review to articles describing primary prevention interventions solely, or primary preventive interventions in combination with secondary, tertiary, or both.

Search results were then cross-compared with a 2003 review of the prevention of occupational asthma,<sup>2</sup> and three reviews of the prevention, identification, and management of occupational asthma that became available during our project period: a comprehensive review commissioned by the British Occupational Health Research Fund,<sup>1</sup> another by an Italian research group,<sup>3</sup> and a web based review and resource on the prevention of occupational asthma launched in October 2005 by the US National Institute for Occupational Safety and Health (NIOSH).<sup>4</sup>

### Causal inference and overall evidence ratings

We rated individual studies using a previously developed causal inference rating scheme for intervention studies.<sup>5-6</sup> We applied a minimum research rating of 3\* (three stars): 3\* = evidence obtained without a control group or randomisation but with evaluation; 4\* = evidence obtained from a properly conducted study with pre and post measures and a control group but without randomisation; 5\* = evidence obtained from a properly conducted study with pre and post measures and evaluation methods (measures, comparison groups, study design) are tabulated along with principal findings in table 1. These ratings and those below were made based on the opinions of 2–3 authors, with final ratings based on consensus where initial ratings differed.

We rated the evidence overall using the revised system of the Scottish Intercollegiate Guidelines Network (SIGN) ([www.sign.ac.uk](http://www.sign.ac.uk)), as was applied in the most recent occupational asthma systematic review<sup>1</sup> and in the British Guidelines on the Management of Asthma ([http://www.brit-thoracic.org.uk/Guidelinesince%201997\\_asthma.html](http://www.brit-thoracic.org.uk/Guidelinesince%201997_asthma.html)). This is a revised version of the system developed by the US Agency for Health Care Policy and Research. The levels of evidence are graded as shown in table 2.

### RESULTS

Natural rubber latex (NRL) was the single most common agent addressed in published occupational asthma primary preventive intervention studies (eight reports). There was a range of study designs applied, ranging from low (cross-sectional) to moderate (prospective cohort) to high (cross-over) causal inference ratings. Methodological limitations included small sample sizes, lack of statistical analyses of observed differences, and the use of prevalence instead of incidence outcome measures. Interpretability was in some cases limited by insufficient detail on the interventions, as well as the fact that many primary interventions were combined with secondary preventive interventions.

We identified five intervention studies on latex<sup>7-11</sup> in addition to those reviewed by Nicholson *et al*<sup>12-14</sup> (table 1). One of these described the same intervention as presented in Tarlo *et al* 2001<sup>14</sup> for illustrative purposes in the context of a province-wide study of Workers' Compensation claims for NRL occupational asthma. The 2001 Tarlo *et al* report was previously reviewed by Nicholson *et al*,<sup>10</sup> thus yielding a total of seven interventions summarised in table 1. Two of the newly identified studies were of high quality and interpretability. The first was a cross-over study which conclusively showed that substitution of powdered NRL gloves with low protein powder-free gloves reduced NRL aeroallergens by 10-fold or more,<sup>7</sup> down to levels comparable to those estimated as a threshold for latex sensitisation in healthcare workers.<sup>15</sup> The second was a prospective cohort study showing that replacement of powdered NRL gloves with low protein powder-free gloves prevented NRL sensitisation.<sup>8</sup> No dental student who was free of latex allergy at baseline (60 of 63) went on to develop latex allergy over four years of follow up, despite likely incidental exposures from other uses of latex in dentistry. This study also provides further support for NRL sensitisation and occupational asthma being almost solely due to powdered NRL glove use.<sup>16</sup> A similar finding—that latex allergy was absent in dental students without a history of powdered latex glove compared to users (13% prevalence)—was made previously, but using a lower causal inference retrospective cross-sectional design.<sup>13</sup> Another study of dental students in Canada also showed a significant reduction in the cross-sectional prevalence of NRL sensitisation, from 10% to 3%, as well as a significant reduction in

NRL related symptoms five years after a change from high protein/powdered to low protein/powder-free latex gloves.<sup>11, 17</sup>

Two studies previously reviewed by Nicholson *et al* were of lower causal inference, but importantly showed the feasibility and effectiveness of glove substitution at the hospital and healthcare system<sup>12</sup> levels. The first showed that hospital-wide substitution of powdered NRL gloves with powder-free gloves at a large Canadian teaching hospital incurred little increase in glove costs (2–3% over four years) and was associated with reduced costs from lost work time and Workers' Compensation claims.<sup>14</sup> The second was a very large German study including approximately 3 million healthcare workers covered by a statutory accident insurance company for healthcare workers; it showed that a system-wide steep decline in usage of powdered NRL gloves was followed by a steep decline in suspected cases of NRL sensitisation and asthma after a two year lag time.<sup>12</sup>

Taken together, these studies support the following evidence statement:

- Substitution of powdered latex gloves with low protein powder-free NRL gloves or latex-free gloves greatly reduces NRL aeroallergens, NRL sensitisation, and NRL asthma in healthcare workers. Evidence rating: SIGN 2+.

### DISCUSSION

This systematic review has shown that there is adequate evidence that primary preventive interventions to reduce the incidence of latex-related sensitisation and occupational asthma can be effective. The quality and quantity of the evidence is not high by typical standards of evidence used in systematic reviews of clinical interventions (only one randomised design in the six studies reviewed). Nevertheless, we would argue that the evidence available is more than adequate justification for substituting powdered latex gloves with low protein powder-free NRL gloves or latex-free gloves, given the challenges of conducting intervention studies in naturalistic settings,<sup>18</sup> and our belief in the appropriateness of applying the precautionary principle in occupational health.<sup>19</sup> Notably, most interventions focused on exposure reduction or elimination, using either sensitisation or quantitative exposure measure outcomes. One exception was the study of Lee *et al*,<sup>9</sup> which showed that substitution focused studies can be feasible, effective, and relatively low cost in instances where the outcome is a simple binary assessment of substitution with a safer alternative. Our review did not identify any evidence to counter Nicholson *et al*'s evidence statements 18 and 19<sup>1</sup> indicating that primary prevention interventions aimed at lowering the susceptibility of the exposed workforce are not effective, thus reinforcing the primacy of exposure reduction or elimination as the intervention of choice.

Despite existing evidence of latex hazards as well as the availability of effective and low cost interventions to address them, recent studies suggest that uptake and action on this message in the healthcare industry is still incomplete.<sup>16, 20</sup> Anecdotal evidence suggests that large acute care hospitals are the most likely to have addressed latex hazards, but systematic study would be required to identify and prioritise other settings still in need of intervention. The high effectiveness of the intervention in health terms, the low cost and high feasibility of the intervention, and the potential Workers' Compensation and other costs savings should make this highly appealing to employers, trade unions, the Workers' Compensation agencies, and other stakeholders.

### Implications for policy and practice

Substitution of powdered latex gloves with low protein powder-free NRL gloves or latex-free gloves promises benefits

**Table 1** Primary preventive intervention studies of natural rubber latex (NRL)

Study; population and sample size	Intervention level, duration (if available)	Intervention description	Evaluation measures, comparison groups	Study design and causal inference rating (3–5 stars)	Principal findings
Allmers <i>et al.</i> , 2002 <sup>12</sup> German workers covered by the statutory accident insurance company for healthcare (responsible for accident insurance, Workers' Compensation, and preventive measures) ~3 million healthcare workers in an unspecified number of hospitals and other healthcare workplaces (Germany)	Primary	Combined policy, education, and regulatory campaign in German healthcare sector, primary focus on substitution of powdered latex gloves to powder-free and low allergen gloves 6 years from first policy recommendations through end of follow-up period	Suspected cases of natural rubber latex (NRL) allergies and occupational asthma (OA) Glove use data projected from a sample of 280 hospitals	Longitudinal, ecologic 3*	Steep decline in usage of powdered NRL gloves in German healthcare sector, especially in acute care hospitals during and following intervention; Steep decline in usage of powdered NRL gloves followed by a steep decline in suspected cases of NRL caused OA after a 2 year lag time Conclusion: substitution of powdered NRL gloves with powder-free and low allergen gloves prevents NRL OA
Heilman <i>et al.</i> , 1996 <sup>7</sup> One operating room (USA)	Primary	Substitution: Alternating use of low allergen containing (powder-free) gloves versus high allergen containing gloves	Latex aeroallergen levels (ng/m <sup>3</sup> ) and extractable latex glove allergen contents in an operating room measured on 52 consecutive days, including 19 non-surgery days On 33 surgery days, all personnel wore either high allergen gloves (n = 18 days) or low allergen gloves (n = 15 days) Internal comparison (cross-over)	Prospective cross-over trial, with 12 (random) cross-overs between low allergen and high allergen glove use 5*	Aeroallergen levels during low allergen glove use days significantly lower than on high allergen glove use days (mean 1.1 versus 13.7 ng/m <sup>3</sup> ), including after adjustment for operating time and amount of gloves used Aeroallergen levels strongly correlated with total number of gloves used on high allergen glove use days, and there was little carryover of aeroallergen levels from one day to the next Conclusion: operating room levels of latex aeroallergen can be reduced tenfold by the use of low allergen gloves instead of high allergen gloves in a typical OR setting
Jones <i>et al.</i> , 2004 <sup>8</sup> Cardiff dental school; n = 63 dental students (UK)	Primary 4 years	Powdered latex gloves replaced with low protein powder-free gloves in 1997	Latex sensitivity determined by skin prick testing with NRL extract, cross-reacting fruits, and other common allergens Skin prick testing done annually over 4 years	Prospective, longitudinal 3*	Initial testing identified 3 incoming students with latex allergy No student who was free of latex allergy at baseline went on to develop latex allergy over the 4 years Conclusion: substitution of nitrile gloves prevents latex sensitisation despite other incidental uses of latex materials in dentistry
Lee <i>et al.</i> , 2001 <sup>9</sup> Food handlers 30 food stalls in Queen Victoria Market, Melbourne (Australia)	Primary Brief in-person educational intervention following baseline assessment	In-person delivery and explanation of a plain language information sheet advising against the use of latex gloves in food handling, out of concern both for customers with latex allergy as well as for workers	Use of latex gloves (10 of 30 stalls assessed were using latex gloves at baseline) 6 weeks and 10 weeks follow-up No comparison groups	Prospective cohort 3*	9 of 10 stalls that were using latex gloves at baseline had discontinued use at 10 weeks post-intervention follow-up (p = 0.006)
Levy <i>et al.</i> , 1999 <sup>13</sup> 103 graduating (5th year) dental students (Paris) and 86 clinical dental students (London); n = 189 (France and UK)	Primary	Use of powdered, protein rich natural rubber latex gloves (n = 96) versus use of powder-free gloves exclusively (n = 93)	History of glove use (frequency and type) over preceding 22 months determined by questionnaire Latex sensitivity determined by skin prick testing with NRL extract	Cross-sectional, retrospective 3*	Zero prevalence of latex sensitivity among those without history of regular powdered glove use (n = 93) versus 13% (11/85) among those who used powdered NRL gloves Results suggest that use of powder free gloves prevents sensitisation and thus NRL related OA

Table 1 Continued

Study; population and sample size	Intervention level, duration (if available)	Intervention description	Evaluation measures, comparison groups	Study design and causal inference rating (3–5 stars)	Principal findings
Saary <i>et al</i> , 2002 <sup>11</sup> and Tarlo <i>et al</i> , 1997 <sup>17</sup> Students (n = 61) and staff (n = 36) of a dental school (Toronto)	Primary Five years	Change from high protein/powdered to low protein/powder-free NRL gloves	Latex sensitivity determined by skin prick testing with NRL extract Asthma symptoms, rhinitis of conjunctivitis, urticaria, and pruritus were determined within minutes of skin-prick NRL exposure	Longitudinal comparisons of cross-sectional prevalence at time 1 <sup>17</sup> versus time 2 <sup>11</sup> 3*	NRL sensitisation significantly decreased at time 2 (3%) in comparison to time 1 (10%) Overall symptoms consistent with IgE mediated responses to NRL gloves significantly reduced at time 2 (12%) in comparison to time 1 (27%) Reductions could not be explained on the basis of time 1 and time 2 differences in demographics, personal or family history of atopy, or work practice variables Results suggest that glove substitution can lead to significant reduction in both NRL related symptoms and sensitisation
Tarlo <i>et al</i> , 2001 <sup>14</sup> and Liss <i>et al</i> , 2001 <sup>10</sup> A large, 2-site teaching hospital 8000 employees, including 2500 nurses, 400 lab technicians, and 350 housekeeping staff (Canada)	Primary 1995 and 1997 Secondary 1994 Tertiary 1985	Conversion to low protein powder-free natural rubber latex (NRL) gloves Education and voluntary medical surveillance Non-NRL gloves provided to allergic workers	Cases of NRL allergy Patterns of glove use	Retrospective, longitudinal 3*	Cases of NRL allergy rose with powdered NRL glove use and peaked with introduction of medical surveillance programme. Cases dropped steadily following the substitution of powdered NRL gloves with powder-free gloves Conclusions limited: essentially a descriptive case study, with numbers too small to support statistical analysis Anecdotally (not systematically assessed in study), other benefits included no additional glove costs (2–3% increase over 4 years) and reduction in hospital expenses from lost work time and Workers' Compensation claims (no NRL allergy related claims since 1995)



**Table 2** Levels of evidence

Grade	Level of evidence
1++	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance, and a moderate probability that the relationship is causal
2–	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

### Main messages

- Substitution of powdered latex gloves with low protein powder-free NRL gloves or latex-free gloves greatly reduces NRL aeroallergens, NRL sensitisation, and NRL asthma in healthcare workers.
- A modest evidence base can be adequate to support evidence statements and recommendations for policy and practice in occupational health.

### Policy implications

- Substitution of powdered latex gloves with low protein powder-free NRL gloves or latex-free gloves promises benefits to worker health as well as cost and human resource savings for employers.
- This message should be broadly disseminated beyond the hospital sector to include other healthcare settings (such as aged care facilities) as well as food service and other industries where latex gloves might be used.

in terms of both workers' health and cost and human resource savings for employers. In addition to hospital settings, this message is relevant to other healthcare organisations (such as aged care facilities) as well as food service and other industries where latex gloves may be used. For non-healthcare settings, communication messages should also emphasise that latex gloves of any sort (even low protein, powder-free) may not be necessary or appropriate. Further, the value of reduced protein and powder in latex gloves is not restricted to primary prevention, since such changes in glove use can also permit accommodation of sensitised (already affected) workers, enabling them to return to work in some cases (tertiary prevention).

In evaluating NRL sensitisation, dermatitis, and asthma in healthcare workers, clinicians should be aware of the potential for multiple allergies,<sup>21</sup> and for latex glove allergy to be due to sensitisation to ethylene oxide used to sterilise the gloves rather than to the latex itself.<sup>22</sup> Practitioners are referred to the recent NIOSH website on the prevention of occupational asthma for further practical guidance.<sup>4</sup> Similar systematic reviews may be feasible for other prevalent occupational asthmagens with accumulating intervention study evidence bases, such as laboratory animal dander, detergent enzymes, and wood dust. Prioritised funding of one or more experimental studies in these areas, as in the case reviewed in this paper, could efficiently confirm the

predominantly observational study evidence base, thus providing more compelling information for action.

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